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detecting the reporter labels of ligated product sequences captured to the solid support at particular sites, thereby indicating the presence of one or more target nucleotide sequences in the sample.

44. (Twice Amended) A method according to claim 1, wherein said subjecting achieves, for a particular oligonucleotide probe set, a rate of formation of [mismatched] ligated product sequences that are mismatched at the site where the oligonucleotide probes for a particular oligonucleotide probe set are ligated which is less than .005 of the rate of formation of matched ligated product sequences for the particular oligonucleotide probe set.

81. (Thrice Amended) A method according to claim 80, wherein each capture oligonucleotide differs from its adjacent capture oligonucleotide on the array by at least one out of every four of the total number of nucleotides when the oligonucleotides are aligned at one [end to] end with one another without internal insertion or deletion.

REMARKS

In view of the above amendments and the following remarks, reconsideration of the final rejection in the parent application is respectfully traversed.

The rejection of claims 1-5, 11-21, 24-43, 45-66, 75-77, 79-80, 83, 87-88, and 138-147 under 35 U.S.C. § 103 for obviousness over Wiedmann, et. al., "Ligase Chain Reaction (LCR)—Overview and Applications," PCR Methods and Applications pp. S51-S64 (1994) ("Wiedmann") in view of Barany, "The Ligase Chain Reaction in a PCR World," PCR Methods and Applications pp. 5-16 (1991)("Barany PCR"), U.S. Patent No. 5,415,839 to Zaun et. al. ("Zaun"), and Guo, et. al, "Direct Fluorescence Analysis of Genetic Polymorphisms by Hybridization with Oligonucleotide Arrays on Glass Supports," Nucl. Acids Res. 22(24): 5456-65 (1994)("Guo") is respectfully traversed in view of the above amendments.

Wiedmann describes the use of the ligase chain reaction ("LCR") procedure to detect single base differences in target nucleic acids. LCR is disclosed to involve the use of 2 pairs of oligonucleotide probes. The first pair of probes is configured to hybridize to a first nucleic acid strand, while the second pair of probes is designed to hybridize to a second

nucleic acid strand complementary to the first nucleic acid strand. The first and second pair of oligonucleotide probes are complementary to one another. As a result of using both pairs of oligonucleotide probes targeted to complementary nucleic acid strands, the LCR procedure is able to achieve exponential amplification. Wiedmann distinguishes the LCR procedure from the ligase detection reaction ("LDR") technique by virtue of the fact that LDR only uses a single pair of oligonucleotide probes which will hybridize to only one target nucleic acid strand and, thus, achieve linear amplification. There is no suggestion in this reference of using LDR in conjunction with a solid support to capture ligated product sequences resulting from LDR by hybridization to a capture oligonucleotide.

Barany PCR is substantially the same as Wiedmann with the former being relied upon in the outstanding office action as teaching signal to noise ratios, various reporter groups, multiplex formats, detection of multiple mutations, operating conditions, and the use of thermostable ligases. Like Wiedmann, Barany PCR does not suggest using LDR in conjunction with a solid support to capture ligated product sequences resulting from LDR by hybridization to a capture oligonucleotide.

Zaun discloses an apparatus and method for amplifying and detecting target nucleic acids. This procedure involves amplifying with a thermal cycling device and then detecting reaction products on a support having one or more reaction sites. Amplification can be carried out using the polymerase chain reaction ("PCR") or gap-LCR procedures. The entire focus of Zaun is the amplification of target nucleic acids—not the detection of single base differences, as claimed. Indeed, as pointed out in applicants' June 15, 1998, Amendment, with regard to the sickle cell anemia situation, Zaun's suggestion that gap-LCR can be employed forecloses any assertion that Zaun's technique is used to detect single base differences. To capture amplification products, the detection system is provided with a support having a plurality of capture sites to immobilize such products on the support. Zaun discloses capturing amplification products with antibody-antigen binding. The presence of captured nucleic acids is revealed by detection of a label bound to the nucleic acid with a specific binding pair, such as antibody-antigen binding, chemical bonding, or complementary polynucleotide procedures. See col. 14, lines 11-25 and col. 32, lines 21-53. There is no enabling disclosure in Zaun of utilizing an LDR procedure for detecting single base changes, insertions, deletions, or translocations, "a first oligonucleotide probe, having an oligonucleotide target-specfic portion and an oligonucleotide addressable array-specific portion, wherein the oligonucleotide addressable array-specific portion is separate and

distinct from the oligonucleotide target-specific portion" where the separate and distinct addressable array-specific portions can hybridize to capture oligonucleotides on a solid support in a base-specific manner.

Guo relates to a multiplex PCR amplification procedure. This involves amplifying and detecting target nucleic acids using fluorescently labeled tags where the amplification products are denatured to render them single stranded, captured on a solid support with oligonucleotide probes, and detected. Like Wiedmann and Barany PCR, Guo does not suggest using LDR in conjunction with a solid support to capture ligated product sequences resulting from LDR by hybridization to a capture oligonucleotide.

Thus, neither Wiedmann, Barany PCR, Zaun, nor Guo suggest using an LDR procedure along with oligonucleotide probe sets where one probe has "an oligonucleotide target-specific portion and an oligonucleotide addressable array-specific portion, wherein the oligonucleotide addressable array-specific portion is separate and distinct from the oligonucleotide target-specific portion", as claimed. The combination of these references also fails to suggest a detection procedure involving capture of the resulting ligated product sequence by hybridization of the separate and distinct addressable array-specific portion to a capture oligonucleotide. In fact, Guo teaches away from the present invention by using an address which is complementary to the target nucleic acid. Accordingly, the rejection based upon this combination of references should be withdrawn.

It is further submitted that this combination of references also fails to teach the parenthetical features of the following dependent claims: 4 (mismatch at a base adjacent to a base at the ligation junction), 11 (quantifying target nucleotide sequences), 12, and 14-34 (detecting multiple allele differences), and 13 (target specific portions of oligonucleotide probes with substantially the same melting temperatures). Therefore, the rejection of claims 4 and 11-34 based on the combination of Wiedmann, Barany PCR, Zaun, and Guo should be withdrawn.

The rejection of claims 6-10, 22, and 23 under 35 U.S.C. § 103 for obviousness over Wiedmann in view of Barany PCR, Zaun, Guo, and Telenti, et. al., "Competitive Polymerase Chain Reaction Using an Internal Standard: Application to the Quantitation of Viral DNA," J. Virol. Methods 39: 259-68 (1992)("Telenti") is respectfully traversed.

Telenti is cited as teaching that PCR can be quantitated by providing a known amount of an internal standard. However, this reference does not disclose the use of an

internal standard in conjunction with an LDR process, nor does it involve the use of arrays. Therefore, Telenti does not overcome the above-noted deficiencies of Wiedmann, Barany PCR, Zaun, and Guo.

The rejection of claim 44 under 35 U.S.C. § 103 for obviousness over Wiedmann in view of Barany PCR, Zaun, Guo, and Barany, "Genetic Disease Detection and DNA Amplification Using Cloned Thermostable Ligase," Proc. Natl. Acad. Sci. USA 88: 189-93 (1991) ("Barany PNAS") is respectfully traversed.

Barany is cited for its teaching of LDR mismatched:matched ratios. However, this reference is substantially similar to Wiedmann and Barany PCR and, therefore, cannot overcome the above-noted deficiencies of Wiedmann, Barany PCR, Zaun, or Guo. Therefore, the rejection of claim 44 should be withdrawn.

The rejection of claims 78, 82, and 84-86 under 35 U.S.C. § 103 for obviousness over Wiedmann in view of Barany PCR, Zaun, Guo, and Sambrook, et. al., Molecular Cloning (1989)("Sambrook") is respectfully traversed.

Sambrook is cited for its teachings regarding hybridizing to immobilized nucleotides, barrier oligonucleotides, exonucleases to destroy nucleotides, and stripping blots. However, Sambrook does not involve the use of LDR in conjunction with arrays and does not overcome the above-noted deficiencies of Wiedmann, Barany PCR, Zaun, Guo, and Sambrook. Accordingly, the rejection of claims 78, 82, and 84-86 should be withdrawn.

The rejection of claims 12, 16, 18-20, 22, 26, 30, 34, and 44 under 35 U.S.C. § 112 (second para.) is respectfully traversed in view of the above amendments.

As to claims 12, 16, 18-20, 22, 26, 30, and 34, applicants submit that the phrase "nucleotide positions which require overlapping probe sets" is fully apparent to one of ordinary skill in the art. As shown, for example, in Figures 5, 7, and 8 and the accompanying text in the specification, it may be necessary to detect single nucleotide differences at several locations proximate to one another with regard to how they hybridize to target nucleic acid sequences during an LDR procedure. As a result, several oligonucleotide probe sets must be used which overlap each other. Accordingly, in view of the disclosure of the present application, applicants submit that claims 12, 16, 18-20, 22, 26, 30, and 34 satisfy the requirements of Section 112.

In the final rejection, the PTO-1449 forms accompanying the Information Disclosure Statement filed simultaneously with the present application were only partly initialed, because the references that were not initialed were said not to have been provided.

Applicants submit that these references have been sent to the PTO at least once and, therefore, it is respectfully requested that the references be located and considered so that the PTO-1449 form can be fully initialed. If these references again need to be filed, it is requested that applicants' undersigned attorney be so notified.

In view of all the foregoing, it is submitted that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

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